REMARKS/ARGUMENTS

Claims 21-34, 45, and 46 are now pending in the application as entered with the Amendment filed March 15, 2004. No further claim amendments are presented herein. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Rejections of the Claims Under 35 U.S.C. §102 Should Be Withdrawn

Claims 21-34, 45, and 46 are rejected under 35 U.S.C. §102(b) as being anticipated by Clark *et al.* (U.S. Patent No. 5,597,802; hereinafter the '802 patent). This rejection is respectfully traversed.

Applicants' invention is directed to IGF-I-containing compositions that comprise a buffer that consists substantially of succinate within a concentration range of about 10 mM to about 40 mM and a counterion (claims 21-34) or succinate within a concentration range of 7 mM to 45 mM and a counterion (claims 45 and 46) . The '802 patent teaches IGF-I compositions useful for administering IGF-I separately from growth hormone (GH) and for admixing with a GH solution to prepare an IGF-I+GH composition. The Office Action points to column 12, lines 14-35, and column 13, lines 16-24, in support of the argument that the '802 patent teaches an IGF-I-containing composition comprising a succinate buffer having a concentration of about 5 to 100 mM and a pH of about 5 to 6, and hence anticipates claims 21-32, 45, and 46. Dependent claims 33 and 34 are further rejected in view of the '802 patent's reference to its IGF-I containing compositions being a liquid or lyophilized powder. Applicants respectfully disagree.

The '802 patent does not recite any concentration limitation for a succinate buffer and only mentions succinate buffer briefly in the following two passages:

> The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; glycine; amino acids such as glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium;

> nonionic surfactants such as polysorbates, poloxamers, or PEG; and/or neutral salts, e.g., NaCl, KCl, $MgCl_2$, $CaCl_2$, etc..

('802 patent, column 11, lines 41-58); and

> The "buffer" may be any suitable buffer that is GRAS and confers a pH of 5-6 on the GH+IGF-I formulation and a pH of about 5-5.5 on the IGF-I formulation. Examples include acetic acid salt buffer, which is any salt of acetic acid, including sodium acetate and potassium acetate, succinate buffer, phosphate buffer, citrate buffer, or any others known to the art to have the desired effect. *The most preferred buffer is sodium acetate, optionally in combination with sodium citrate.*

('802 patent, column 13, lines 16-24; emphasis added). These passages fail to teach all the limitations of the presently claimed invention as there is no disclosure of an IGF-I-containing composition formulated with a buffer that consists substantially of succinate at a concentration of about 10 mM to about 40 mM and a counterion or a buffer that consists substantially of succinate at a concentration of 7 mM to 45 mM.

The Office Action cites to column 12, lines 14-35, of the '802 patent in support of this §102 rejection. This passage of the '802 patent discloses a particularly preferred embodiment wherein the composition comprises IGF-I and GH and "about 5 to 100 mM of *a* [emphasis added] buffer at or about pH 5-6." In the context of this embodiment, there is no mention of any particular buffering agent to be used at this concentration range, much less a specific disclosure of the use of succinate buffer at a concentration of about 5 to 100 mM as the Examiner has asserted. This generic disclosure of the use of a broad concentration range of "a buffer" does not teach all of the limitations of the presently claimed invention, particularly when the teachings of this cited reference *as a whole* are taken into consideration.

Applicants respectfully submit that the Examiner has improperly relied upon the generalizations as to suitable buffers taught elsewhere in the '802 patent to construe this particular passage at column 12 as being anticipatory for the presently claimed invention. A closer reading of this patent reveals that the IGF-I compositions disclosed therein are preferably formulated with *an acetic acid salt buffer*, and *most preferably sodium acetate*. See the '802 patent at column 14, lines 12-30, and at column 14, lines 31-44, where the most preferred IGF-I formulation is taught. The '802 patent in fact teaches that the IGF-I formulation to be mixed with

the GH solution preferably uses *50 mM sodium acetate* to ensure that the final pH in the IGF-I+GH mixture will not vary significantly from pH 5.4 to maintain solubility of both proteins (column 14, lines 38-42). See also Examples IV-XIV of this patent, which describe the increased potency and efficacy of IGF-I and/or IGF-I+GH compositions formulated with sodium acetate buffer. One of skill in the art would therefore conclude that the particularly preferred IGF-I+GH composition comprising "about 5 to 100 mM of a buffer at or about pH 5-6" taught at column 12, lines 14-35, of this cited patent would be formulated with an acetic acid salt buffer, most preferably sodium acetate, in the starting IGF-I solution, and therefore would comprise this particular buffer in the final IGF-I+GH composition.

In contrast, the presently claimed invention is drawn to IGF-I compositions that are formulated in a *succinate buffer* with a concentration that ranges, at the broadest, from 7 mM to 45 mM. Applicants' respectfully submit that the '802 patent does not teach this concentration limitation for a succinate buffer for all of the reasons noted above. Accordingly, the '802 patent is not an anticipatory reference, and this rejection of the claims should be withdrawn.

Claims 21-34 and 45-46 are rejected under 35 U.S.C. §102(e) as being anticipated by Clark *et al.* (U.S. Patent No. 5,783,556; hereinafter the '556 patent). This rejection is respectfully traversed.

As noted above, Applicants' invention is directed to IGF-I-containing compositions that comprise a buffer that consists substantially of succinate at a concentration of about 10 mM to about 40 mM and a counterion (claims 21-34) or succinate within a concentration range of 7 mM to 45 mM and a counterion (claims 45 and 46). The '556 patent teaches IGF-I compositions useful for administering IGF-I separately from long-acting neutral protamine hagedorn (NPH) insulin and for admixing with an NPH insulin solution to prepare an IGF-I+NPH insulin composition. The Office Action cites to column 12, lines 13-37, and column 13, lines 18-29, of the '556 patent in support of the argument that the '556 patent teaches an IGF-I-containing composition comprising a succinate buffer having a concentration of about 5 to 100 mM and a pH of about 5 to 6, and hence anticipates claims 21-32. Claims 33 and 34 are further rejected in in view of the '556 patent's reference to its IGF-I containing compositions being a liquid or

lyophilized powder. Finally, claims 45 and 46 are further rejected in view of this cited patent's reference to its IGF-I containing compositions being sterile and suitable for injection. Applicants respectfully disagree for reasons similar to those noted for the rejection of these claims under the '802 patent.

Similar to the '802 patent, the '556 patent does not recite any concentration limitation for a succinate buffer and only mentions succinate buffer briefly in the following two passages:

> The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; glycine; amino acids such as glutamic acid, aspartic acid, histidine, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, trehalose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counter-ions such as sodium; non-ionic surfactants such as polysorbates, poloxamers, or polyethylene glycol (PEG); and/or neutral salts, e.g., NaCl, KCl, $MgCl_2$, $CaCl_2$, etc.

('556 patent, column 11, line 55, continuing through column 12, line 13); and

> The "buffer" may be any suitable buffer that is GRAS and generally confers a pH from or about 4.8 to 8, preferably from or about 5 to 7, more preferably from or about 5 to 6, on the NPH insulin+IGF-I formulation, and preferably a pH of from or about 5 to 6, more preferably from or about 5 to 5.5, on the IGF-I formulation. Examples include acetic acid salt buffer, which is any salt of acetic acid, including sodium acetate and potassium acetate, succinate buffer, phosphate buffer, citrate buffer, histidine buffer, or any others known to the art to have the desired effect. *The most preferred buffer is sodium acetate, optionally in combination with sodium phosphate.*

('556 patent, column 13, lines 18-29; emphasis added). These passages fail to teach all the limitations of the presently claimed invention as there is no disclosure of an IGF-I-containing composition formulated with a buffer that consists substantially of succinate at a concentration of about 10 mM to about 40 mM and a counterion or a buffer that consists substantially of succinate at a concentration of 7 mM to 45 mM.

The Office Action cites to column 12, lines 13-37, of the '556 patent in support of this §102 rejection. This passage of the '556 patent discloses a particularly preferred embodiment

wherein the composition comprises IGF-I and NPH insulin and "about 5 to 100 mM of *a* [emphasis added] buffer at or about pH 5-6." As for the '802 patent, in the context of this preferred embodiment, there is no mention of any particular buffering agent to be used at this concentration range, much less a specific disclosure of the use of succinate buffer at a concentration of about 5 to 100 mM as the Examiner has asserted. This generic disclosure of the use of a broad concentration range of "a buffer" does not teach all of the limitations of the presently claimed invention, particularly when the teachings of this cited reference *as a whole* are taken into consideration.

Applicants respectfully submit that the Examiner has improperly relied upon the generalizations as to suitable buffers taught elsewhere in the '556 patent to construe this particular passage at column 12 as being anticipatory for the presently claimed invention. A closer reading of this patent reveals that the IGF-I compositions disclosed therein are preferably formulated with *an acetic acid salt buffer*, and *most preferably sodium acetate*. See the '556 patent at column 14, lines 1-20, particularly lines 6-7; and at column 14, lines 21-38, where the most preferred IGF-I formulation is taught. The '556 patent in fact teaches that the IGF-I formulation to be mixed with the NPH insulin solution preferably uses *50 mM sodium acetate* to ensure that the final pH in the IGF-I+NPH insulin mixture will not vary significantly from pH 5.4 to maintain high solubility of IGF-I and low solubility of NPH insulin (column 14, lines 32-36). Furthermore, the kits disclosed in the patent contain IGF-I in a pharmaceutically acceptable *acetic acid salt buffer* (column 14, lines 39-62; emphasis added). See also Examples I and II, particularly the summary at column 20, lines 52-62, stating the preferred method of delivery for the IGF-I+NPH insulin composition is using an IGF-I acetate-buffered formulation. One of skill in the art would therefore conclude that the particularly preferred IGF-I+NPH insulin composition comprising "about 5 to 100 mM of a buffer at or about pH 5-6" taught at column 12, lines 14-35, of this cited patent would be formulated with an acetic acid salt buffer, most preferably sodium acetate, in the starting IGF-I solution, and therefore would comprise this particular buffer in the final IGF-I+NPH insulin composition.

In contrast, the presently claimed invention is drawn to IGF-I compositions that are formulated in a *succinate buffer* with a concentration that ranges, at the broadest, from 7 mM to

45 mM. Applicants' respectfully submit that the '556 patent does not teach this concentration limitation for a succinate buffer for all of the reasons noted above. Accordingly, the '556 patent is not an anticipatory reference, and this rejection of the claims should be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §102(b) and §102(e) are overcome. Accordingly, the present application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on July 12, 2004.

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